

**Amendments to the Claims:**

Please add claims 45-98. This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. (Original) A method to produce a human immunoglobulin or an analog thereof, specific for a desired antigen, which method comprises:

administering said antigen or an immunogenic portion thereof to a nonhuman animal under conditions to stimulate an immune response, whereby said animal produces B cells that secrete immunoglobulin specific for said antigen; wherein said nonhuman animal is characterized by being substantially incapable of producing endogenous heavy and light immunoglobulin chains, but capable of producing human immunoglobulin; and

recovering said immunoglobulin or analog.

2. Canceled.

3. (Original) The method of claim 1 wherein said recovering step comprises immortalizing B cells from said animal immunized with said antigen, screening the resulting immortalized cells for the secretion of said immunoglobulin specific for said antigen, and

a) recovering immunoglobulin secreted by said immortalized B cells, or

b) recovering the genes encoding at least the immunoglobulin from the immortalized B cells, and optionally modifying said genes;

expressing said genes or modified forms thereof to produce immunoglobulin or analog; and

recovering said immunoglobulin or analog.

4. (Original) The method of claim 1 wherein said recovering step comprises:

recovering genes encoding the immunoglobulins from the primary B cells of the animal;

generating a library of said genes expressing the immunoglobulins;

screening the library for an immunoglobulin with the desired affinity for the antigen;

recovering the genes encoding the immunoglobulin;

expressing said recovered genes to produce an immunoglobulin or analog recovering said immunoglobulin or analog.

5. (Original) A recombinant DNA molecule comprising a nucleotide sequence encoding the immunoglobulin or analog produced by the method of claim 1.

6. Canceled.

7. (Previously Presented) A cell or cell line modified to contain the DNA molecule of claim 5.

8. (Original) A method to produce a fully human immunoglobulin or an analog thereof which method comprises culturing the cells of claim 7 under conditions whereby said encoding nucleotide sequence is expressed to produce

said immunoglobulin or analog; and recovering said immunoglobulin or analog.

9. (Original) A DNA molecule comprising a nucleotide sequence corresponding to the gene or modified gene prepared by the method of claim 3.

10. Canceled.

11. (Original) A cell or cell line modified to contain the DNA molecule of claim 9.

12. (Original) A method to produce a fully human immunoglobulin or an analog thereof which method comprises culturing the cells of claim 11 under conditions whereby said encoding nucleotide sequence is expressed to produce said immunoglobulin or analog; and recovering said immunoglobulin or analog.

13. (Original) A DNA molecule which comprises a nucleotide sequence encoding a human immunoglobulin with desired affinity prepared according to the method of claim 4.

14. Canceled.

15. (Original) A cell or cell line modified to contain the DNA molecule of claim 13.

16. (Original) A method to produce a fully human immunoglobulin or an analog thereof which method comprises culturing the cells of claim 15 under conditions whereby said encoding nucleotide sequence is expressed to produce said immunoglobulin or analog; and recovering said immunoglobulin or analog.

17. (Original) An immortalized B cell which secretes a fully human immunoglobulin to a desired antigen prepared according to claim 3.

18. (Original) A method to produce an immunoglobulin or analog which comprises culturing the cells of claim 17 and recovering said immunoglobulin or analog.

19. (Original) A fully human immunoglobulin or analog produced by the method of claim 1.

20. (Original) The immunoglobulin or analog of claim 19 wherein the desired antigen is selected from the group consisting of

the leukocyte markers, CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD11a,b,c, CD13, CD14, CD18, CD19, CD20, CD22, CD23, CD27 and its ligand, CD28 and its ligands B7.1, B7.2, B7.3, CD29 and its ligand, CD30 and its ligand, CD40 and its ligand gp39, CD44, CD45 and isoforms, CDw52 (Campath antigen), CD56, CD58, CD69, CD72, CTLA-4, LFA-1 and TCR;

the histocompatibility antigens, MHC class I or II, the Lewis Y antigens, SLex, SLey, SLea, and SLeb;

the integrins, VLA-1, VLA-2, VLA-3, VLA-4, VLA-5, VLA-6,  $\alpha_V\beta_3$ , and LFA-1, Mac-1, and p150,95,  $\alpha_V\beta_1$ , gpIIbIIIa,  $\alpha_R\beta_3$ ,  $\alpha_6\beta_4$ ,  $\alpha_V\beta_5$ ,  $\alpha_V\beta_6$ , and  $\alpha_V\beta_7$ ;

the selectins, L-selectin, P-selectin, and E-selectin and their counterreceptors VCAM-1, ICAM-1, ICAM-2, and LFA-3;

the interleukins, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, and IL-15;

the interleukin receptor is selected from the group consisting of IL-1R, IL-2R, IL-3R, IL-4R, IL-5R, IL-6R, IL-7R, IL-8R, IL-9R, IL-10R, IL-11R, IL-12R, IL-13R, IL-14R, and IL-15R;

the chemokine is selected from the group consisting of PF4, RANTES, MIP1 $\alpha$ , MCP1, NAP-2, Gro $\alpha$ , Gro $\beta$ , and IL-8;

the growth factor is selected from the group consisting of TNF $\alpha$ , TGF $\beta$ , TSH, VEGF/VPF, PTHrP, EGF family, FGF, PDGF family, endothelin, Fibronectin (F $_n$ F $_1$ ), human Laminin, and gastrin releasing peptide (GRP);

the growth factor receptor is selected from the group consisting of TNF $\alpha$ R, TGF $\beta$ R, TSHR, VEGFR/VPFR, FGFR, EGFR, PTHrPR, PDGFR family, EPO-R, G-CSF-R and other hematopoietic receptors;

the interferon receptor is selected from the group consisting of IFN $\alpha$ R, IFN $\beta$ R, and IFN $\gamma$ R;

the Ig and its receptor is selected from the group consisting of IgE, Fc $\epsilon$ R1, and Fc $\epsilon$ R2;

the tumor antigen is selected from the group consisting of her2-neu, mucin, CEA and endosialin;

the allergen is selected from the group consisting of house dust mite antigen, lol p1 (grass) antigens, and urushiol;

the viral protein is selected from the group consisting of CMV glycoproteins B, H, and gCIII, HIV-1 envelope glycoproteins, RSV envelope glycoproteins, HSV envelope glycoproteins, HPV envelope glycoproteins, Hepatitis family surface antigens;

the toxin is selected from the group consisting of pseudomonas endotoxin and osteopontin/uropontin, snake venom, spider venom, and bee venom conotoxin;

the blood factor is selected from the group consisting of complement C3b, complement C4a, complement C4b-9, Rh factor, fibrinogen, fibrin, and myelin associated growth inhibitor; and

the enzyme is selected from the group consisting of cholesterol ester transfer protein, membrane bound matrix metalloproteases, and glutamic acid decarboxylase (GAD).

21. Canceled.

22. (Previously Presented) A recombinant DNA molecule comprising a nucleotide sequence that encodes the immunoglobulin or analog of claim 19.

23. Canceled.

24. (Previously Presented) A cell or cell line modified to contain the DNA molecule of claim 22.

25. (Original) A method to produce an immunoglobulin or analog specific for a desired antigen which method comprises culturing the cell or cell line of claim 24 under conditions wherein said nucleotide sequence is expressed to

produce said immunoglobulin or analog; and recovering the immunoglobulin or analog.

26. (Original) An human antibody or analog thereof which is specifically immunoreactive with an antigen selected from the group consisting of transition state mimics; leukocyte markers; histocompatibility antigens; adhesion molecules; interleukins; interleukin receptors; chemokines; growth factors; growth factor receptors; interferon receptors; Igs and their receptors, tumor antigens; allergens; viral proteins; toxins; blood factors; enzymes; and the miscellaneous antigens ganglioside GD3, ganglioside GB2, LMP1, LMP2, eosinophil major basic protein, eosinophil cationic protein, pANCA, Amadori protein, Type IV collagen, glycated lipids,  $\lambda$ -interferon, A7, P-glycoprotein, Fas (AFO-1) and oxidized-LDL.

27. (Original) The antibody or analog of claim 26 wherein the leukocyte marker is selected from the group consisting of CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD11a,b,c, CD13, CD14, CD18, CD19, CD20, CD22, CD23, CD27 and its ligand, CD28 and its ligands B7.1, B7.2, B7.3, CD29 and its ligand, CD30 and its ligand, CD40 and its ligand gp39, CD44, CD45 and isoforms, CDw52 (Campath antigen), CD56, CD58, CD69, CD72, CTLA-4, LFA-1 and TCR;

the histocompatibility antigen is selected from the group consisting of MHC class I or II, the Lewis y antigens, SLex, SLe<sup>y</sup>, SLe<sup>a</sup>, and SLe<sup>b</sup>;

the adhesion molecule is selected from the group consisting of VLA-1, VLA-2, VLA-3, VLA-4, VLA-5, VLA-6,  $\alpha$ V $\beta$ 3, and LFA-1, Mac-1, p150,95,  $\alpha$ V $\beta$ 1, gpIIbIIIa,  $\alpha$ <sub>R</sub> $\beta$ 3,

$\alpha_6\beta_4$ ,  $\alpha_v\beta_5$ ,  $\alpha_v\beta_6$ , and  $\alpha_v\beta_7$ , L-selectin, P-selectin, and E-selectin and their counterreceptors VCAM-1, ICAM-1, ICAM-2, and LFA-3;

the interleukin is selected from the group consisting of IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, and IL-15;

the interleukin receptor is selected from the group consisting of IL-1R, IL-2R, IL-3R, IL-4R, IL-5R, IL-6R, IL-7R, IL-8R, IL-9R, IL-10R, IL-11R, IL-12R, IL-13R, IL-14R, and IL-15R,

the chemokine is selected from the group consisting of PF4, RANTES, MIP1 $\alpha$ , MCP1, NAP-2, Gro $\alpha$ , Gro $\beta$ , and IL-8;

the growth factor is selected from the group consisting of TNF $\alpha$ , TGF $\beta$ , TSH, VEGF/VPF, Pthrp, EGF family, FGF, PDGF family, endothelia, Fibrosin (F $_s$ F $_{-1}$ ), human Laminin, and gastrin releasing peptide (GRP);

the growth factor receptor is selected from the group consisting of TNF $\alpha$ R, RGF $\beta$ R, TSHR, VEGFR/VPFR, FGFR, EGFR, PTHrPR, PDGFR family, EPO-R, GCSF-R and other hematopoietic receptors;

the interferon receptor is selected from the group consisting of IFN $\alpha$ R, IFN $\beta$ R, and IFN $\gamma$ R;

the Ig and its receptor is selected from the group IgE, Fc $\epsilon$ RI, and Fc $\epsilon$ RII;

tumor antigen is selected from the group her2-neu, mucin, CEA and endosialin;



the allergen is selected from the group consisting of house dust mite antigen, lol p1 (grass) antigens, and urushiol;

the viral protein is selected from the group consisting of CVM glycoproteins B, H, and GCIII, HIV-1 envelope glycoproteins, RSV envelope glycoproteins, HSV envelope glycoproteins, EBV envelope glycoproteins, VZV envelope glycoproteins, HPV envelope glycoproteins, Hepatitis family surface antigens;

the toxin is selected from the group consisting of pseudomonas endotoxin and osteopontin/ uropontin, snake venom, and bee venom;

the blood factor is selected from the group consisting of complement C3b, complement C5a, complement C5b-9, RH factor, fibrinogen, fibrin, and myelin associated growth inhibitor; and

the enzyme is selected from the group consisting of cholesterol ester transfer protein, membrane bound matrix metalloproteases, and glutamic acid decarboxylase (GAD).

28. Canceled.

29. Canceled.

30. Canceled.

31. Canceled.

32. Canceled.

33. Canceled.

34. Canceled.

35. Canceled.

36. Canceled.

37. Canceled.

38. Canceled.

39. Canceled.

40. Canceled.

41. (Previously Presented) A recombinant DNA molecule encoding the antibody of any of claim 26.

42. Canceled.

43. (Previously Presented) A recombinant host cell which is modified to contain the DNA molecule of claim 41.

44. (Original) A method to produce an antibody or analog which method comprises culturing cells of claim 43 under conditions wherein said coding sequence is expressed; and recovery the antibody of analog produced.

45. (New) An isolated human antibody or an antigen-binding fragment thereof that specifically binds a leukocyte marker selected from the group consisting of CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD11a, b, c, CD13, CD14, CD18, CD19, CD20, CD22, CD23, CD27, CD28, CD29, CD30, CD40, CD44, CD45 and isoforms, Cdw52 (Campath antigen), CD56, CD58, CD69, CD72, CTLA-4, LFA-1, and TCR,

wherein said antibody or fragment modulates the activity of said leukocyte marker.

46. (New) The antibody or fragment according to claim 45 wherein the leukocyte marker is CD4.

47. (New) The antibody or fragment according to claim 45 herein the leukocyte marker is CD8.

48. (New) The antibody or fragment according to claim 45 wherein the leukocyte marker is CD28.

49. (New) The antibody or fragment according to claim 45 wherein the leukocyte marker is CD40.

50. (New) The antibody or fragment according to claim 45 wherein the leukocyte marker is CD45.

51. (New) The antibody or fragment according to claim 45 wherein the leukocyte marker is TCR.

52. (New) The antibody according to any one of claims 45-51, wherein the antibody is monoclonal.

53. (New) The fragment according to any one of claims 45-51, wherein the fragment comprises an scFv, Fab, Fab', or F(ab')<sub>2</sub> fragment.

54. (New) The antibody according to any one of claims 45-51, wherein the antibody is detectably labeled.

55. (New) The antibody according to any one of claims 45-51, wherein the leukocyte marker is human.

56. (New) The antibody according to any one of claims 45-51, wherein the antibody decreases activity of the leukocyte marker.

57. (New) The antibody according to any one of claims 45-51, wherein the antibody comprises lambda light chain sequence.

58. (New) The antibody according to any one of claims 45-51, wherein the antibody increases an activity of the leukocyte marker.

59. (New) The antibody according to any one of claims 45-51, further comprising a pharmaceutical formulation.

60. (New) A host cell that expresses the antibody according to any one of claims 45-51.

61. (New) A nucleic acid that encodes the antibody according to any one of claims 45-51.

62. (New) A host cell comprising the nucleic acid of claim 61.

63. (New) A method of producing an isolated human antibody that specifically binds and modulates the activity of a leukocyte marker selected from the group consisting of CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD11a, b, c, CD13, CD14, CD18, CD19, CD20, CD22, CD23, CD27, CD28, CD29, CD30, CD40, CD44, CD45 and isoforms, Cdw52 (Campath antigen), CD56, CD58, CD69, CD72, CTLA-4, LFA-1, and TCR comprising:

(a) administering the leukocyte marker or an immunogenic fragment thereof to a mouse capable of expressing human immunoglobulin;

(b) screening the administered mouse for expression of a human antibody that specifically binds to the leukocyte marker;

(c) selecting a mouse that produces a human antibody that specifically binds to the leukocyte marker;

(d) isolating an antibody from the mouse that produces a human antibody that specifically binds to the leukocyte marker; and

(e) determining whether the antibody modulates an activity of the leukocyte marker thereby producing a human

antibody that specifically binds to the leukocyte marker and modulates an activity of the leukocyte marker.

64. (New) A method of producing an isolated human antibody that specifically binds to and modulates the activity of a leukocyte marker selected from the group consisting of CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD11a, b, c, CD13, CD14, CD18, CD19, CD20, CD22, CD23, CD27, CD28, CD29, CD30, CD40, CD44, CD45 and isoforms, Cdw52 (Campath antigen), CD56, CD58, CD69, CD72, CTLA-4, LFA-1, and TCR comprising:

(a) administering the leukocyte marker or an immunogenic fragment thereof to a mouse capable of expressing human immunoglobulin;

(b) isolating spleen cells from the mouse that produces a human antibody that specifically binds to the leukocyte marker;

(c) fusing the spleen cells with a myeloma cell to produce a hybridoma; and

(d) screening the hybridoma for expression of a human antibody that specifically binds to and modulates an activity of the leukocyte marker thereby producing a human

monoclonal antibody that specifically binds to and modulates an activity of the leukocyte marker.

65. (New) The method according to claim 63 or 64 wherein the leukocyte marker is CD4.

66. (New) The method according to claim 63 or 64 wherein the leukocyte marker is CD8.

67. (New) The method according to claim 63 or 64 wherein the leukocyte marker is CD28.

68. (New) The method according to claim 63 or 64 wherein the leukocyte marker is CD40.

69. (New) The method according to claim 63 or 64 wherein the leukocyte marker is CD45.

70. (New) The method according to claim 63 or 64 wherein the leukocyte marker is TCR.

71. (New) A monoclonal antibody isolated from a hybridoma produced by the method of claim 64.

72. (New) A method for modulating an activity of a leukocyte marker selected from the group consisting of CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD11a, b, c, CD13, CD14, CD18, CD19, CD20, CD22, CD23, CD27, CD28, CD29, CD30, CD40,

CD44, CD45 and isoforms, Cdw52 (Campath antigen), CD56, CD58, CD69, CD72, CTLA-4, LFA-1, and TCR comprising contacting a cell that expresses the leukocyte marker with a modulating amount of the antibody of claim 45.

73. (New) The method according to claim 72 wherein the leukocyte marker is CD4.

74. (New) The method according to claim 72 wherein the leukocyte marker is CD8.

75. (New) The method according to claim 72 wherein the leukocyte marker is CD28.

76. (New) The method according to claim 72 wherein the leukocyte marker is CD40.

77. (New) The method according to claim 72 wherein the leukocyte marker is CD45.

78. (New) The method according to claim 72 wherein the leukocyte marker is TCR.

79. (New) The method of claim 72, wherein the leukocyte marker is human.

80. (New) The method of claim 72, wherein the activity is increased.



81. (New) The method of claim 72, wherein the activity is decreased.

82. (New) A method of increasing an activity of a leukocyte marker selected from the group consisting of CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD11a, b, c, CD13, CD14, CD18, CD19, CD20, CD22, CD23, CD27, CD28, CD29, CD30, CD40, CD44, CD45 and isoforms, Cdw52 (Campath antigen), CD56, CD58, CD69, CD72, CTLA-4, LFA-1, and TCR in a subject comprising administering to the subject an amount of a human antibody that increases an activity of the leukocyte marker.

83. (New) A method of decreasing an activity of a leukocyte marker selected from the group consisting of CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD11a, b, c, CD13, CD14, CD18, CD19, CD20, CD22, CD23, CD27, CD28, CD29, CD30, CD40, CD44, CD45 and isoforms, Cdw52 (Campath antigen), CD56, CD58, CD69, CD72, CTLA-4, LFA-1, and TCR in a subject comprising administering to the subject an amount of a human antibody that decreases an activity of the leukocyte marker.

84. (New) A method of detecting the presence of a leukocyte marker selected from the group consisting of CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD11a, b, c, CD13, CD14,

CD18, CD19, CD20, CD22, CD23, CD27, CD28, CD29, CD30, CD40, CD44, CD45 and isoforms, Cdw52 (Campath antigen), CD56, CD58, CD69, CD72, CTLA-4, LFA-1, and TCR in a sample or a cell, comprising contacting a sample having or suspected of having the leukocyte marker, or a cell expressing or suspected of expressing the leukocyte marker, with the antibody of claim 1, and detecting the presence of the leukocyte marker in the sample or cell.

85. (New) The method according to claim 82, 83 or 84, wherein the leukocyte marker is CD4.

86. (New) The method according to claim 82, 83 or 84 wherein the leukocyte marker is CD8.

87. (New) The method according to claim 82, 83 or 84, wherein the leukocyte marker is CD28.

88. (New) The method according to claim 82, 83 or 84, wherein the leukocyte marker is CD40.

89. (New) The method according to claim 82, 83 or 84, wherein the leukocyte marker is CD45.

90. (New) The method according to claim 82, 83 or 84, wherein the leukocyte marker is TCR.

91. (New) The method of claim 84, wherein the cell is in a subject.

92. (New) A method of detecting the presence of a disorder associated with increased or decreased expression of a a leukocyte marker selected from the group consisting of CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD11a, b, c, CD13, CD14, CD18, CD19, CD20, CD22, CD23, CD27, CD28, CD29, CD30, CD40, CD44, CD45 and isoforms, Cdw52 (Campath antigen), CD56, CD58, CD69, CD72, CTLA-4, LFA-1, and TCR in a human, comprising contacting a sample having or suspected of having the leukocyte marker or a cell expressing or suspected of expressing the leukocyte marker, wherein the sample or cell is from or present in the human, with the human antibody of claim 45 and detecting the presence of increased or decreased expression of the leukocyte marker in the sample or cell relative to a control thereby detecting the presence of a disorder associated with increased or decreased expression of the leukocyte marker in the human.

93. (New) The method according to claim 92, wherein the leukocyte marker is CD4.

94. (New) The method according to claim 92, wherein the leukocyte marker is CD8.

95. (New) The method according to claim 92, wherein the leukocyte marker is CD28.

96. (New) The method according to claim 92, wherein the leukocyte marker is CD40.

97. (New) The method according to claim 92, wherein the leukocyte marker is CD45.

98. (New) The method according to claim 92, wherein the leukocyte marker is TCR.